ORIGINAL ARTICLE

Benefits and harms of roflumilast in moderate to severe COPD

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ABSTRACT

Background Roflumilast, a phosphodiesterase 4 inhibitor, has been approved for the prevention of chronic obstructive pulmonary disease (COPD) exacerbations. It is unclear which patients will have a favourable benefit–harm balance with roflumilast. Our aim was to quantitatively assess the benefits and harms of roflumilast (500 μg/day) compared with placebo.

Methods We used summary data released by the US Food and Drug Administration to estimate the treatment effects of roflumilast. Data from trials and observational studies were used to estimate the baseline risks for COPD exacerbations and gastrointestinal, neurological and psychiatric harms associated with roflumilast. Using simulation, we calculated the probability that roflumilast provides net benefit. We examined the impacts of different baseline risks for exacerbations and the severity of exacerbations, and varied weights (ie, relative importance) for outcomes and treated death as a competing risk in the analyses.

Results The probability that roflumilast provides net benefit approximates 0% across different age categories of men and women with varying baseline risks for exacerbations. Using different weights for outcomes did not change the probability that roflumilast provides a net benefit. Only in the sensitivity analysis restricted to the prevention of severe exacerbations was there a probability of >50% that roflumilast provides a net benefit if the baseline risk of having at least one severe exacerbation per year exceeds 22%.

Conclusions Our results suggest that roflumilast only provides a net benefit to patients at a high risk of severe exacerbations. Guideline developers should consider different recommendations for patients with COPD at different baseline risks for exacerbations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) poses a great burden for patients and healthcare systems because it is a leading cause of mortality and morbidity worldwide.[1] [2] While inhaled drug treatments, pulmonary rehabilitation, long-term oxygen and surgery provide some benefits to patients with COPD,[3] finding additional drug treatments that can effectively target important goals of the management of COPD such as symptom relief and reduction of COPD exacerbations is currently a major focus of research and drug development.[4–7]

Phosphodiesterase 4 (PDE4) inhibitors are among the drugs that have raised hope for more effective COPD treatment. Many phase II and III randomised controlled trials (RCTs) have explored the efficacy and safety of the PDE4 inhibitors roflumilast and cilomilast in patients with COPD. As a result, roflumilast was recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for reducing the risk of exacerbations in patients with severe COPD and a history of exacerbations.[8] [9] Cilomilast was not approved by the FDA or EMA in large part because its benefits did not appear to exceed its harms. A Cochrane systematic review of PDE4 inhibitors in COPD concluded that, while roflumilast reduced the (relative) risk of exacerbations by around 20% compared with placebo, it was indeed associated with harms such as diarrhoea, nausea, depression and weight loss.[10]

Currently, it is still difficult to judge whether or not the benefits of roflumilast outweigh the harms. Clinicians are left with uncertainty about whether or not to recommend roflumilast to patients and whether the balance of benefits and harms varies among subpopulations within the approved population. Judging the benefit–harm balance of roflumilast is challenging because the drug has differential effects on distinct outcomes that are of varying importance to patients and that occur with different frequency. Trial reports and systematic reviews typically provide data on benefit and harm

Key messages

What is the key question?
► What is the benefit–harm balance of roflumilast (500 μg/day) in patients with moderate to severe COPD and a history of exacerbations compared with placebo?

What is the bottom line?
► The benefit–harm balance of roflumilast is only favourable for a small subgroup of patients with COPD at high risk for severe exacerbations and guideline developers should consider different recommendations for and against roflumilast for patients at different risks for moderate or severe exacerbations, respectively.

Why read on?
► This is one of the first benefit–harm assessments of roflumilast that used a quantitative, comprehensive and transparent approach.

outcomes separately, with no attempt to integrate the two types of outcomes.

The aim of this study was to estimate the benefits and harms of roflumilast compared with placebo in patients with COPD giving consideration to multiple outcomes, baseline risks and patient preferences, and using a systematic approach for identifying and synthesising relevant sources of evidence.

METHODS
Definition of the target population, intervention and outcomes

The population of interest included patients with moderate to severe COPD with a history of exacerbations, for whom roflumilast (1×500 μg tablet per day) was approved.[9] The outcomes, evaluated over 1 year, included moderate or severe exacerbations prevented and harms. We defined a moderate exacerbation, following the definition of the manufacturer, as a COPD event requiring outpatient treatment and defined a severe exacerbation as a COPD event resulting in hospitalisation or death.[11] Harm outcomes included gastrointestinal (acute pancreatitis, diarrhoea, nausea and weight loss), psychiatric (insomnia, anxiety, depression and suicide) and neurological (headache and dizziness) symptoms or disorders.

Selection of data sources
Treatment effect estimates

We identified a Cochrane review[10] of PDE4 inhibitors and the FDA documents publicly available online (medical reviews of roflumilast)[11] as the best available data source for estimating the treatment effects of roflumilast. The FDA documents included all data presented in the Cochrane review but provided substantial additional information—for example, on incidence rate ratios and on harm outcomes.

Baseline risks without roflumilast for a time period of 1 year

The baseline risk (the risk for outcomes at treatment initiation) has a large impact on benefit–harm assessment. We relied on observational studies for estimating the baseline risk for outcomes whenever possible because the control group risk in RCTs might not reflect the risk of patients with COPD seen in practice. For some outcomes where we could not find appropriate data from observational studies, we used the risk in the control group of RCTs. Although a time horizon of >1 year would be relevant for patients and physicians, we decided not to do any analyses beyond 1 year because of the absence of trial data on the long-term effects of roflumilast.

Weights (relative importance) for outcomes

We considered that the benefit and harm outcomes are, on average, of different importance to patients. We could not find a study (eg, preference-eliciting survey) that provides weights for all outcomes for our decision-making context. We therefore used various approaches to assigning weights to outcomes in the analysis to explore how they affect the benefit–harm balance.

Statistical analysis

We conducted a benefit–harm assessment of roflumilast following the Gail approach that was developed by the National Cancer Institute to estimate the benefit–harm balance of tamoxifen for the prevention of breast cancer.[12] This approach combines data on treatment effects, baseline risks and relative importance of outcomes to provide a net benefit–harm index for decision-making. For a patient with COPD of a certain age, sex and with a certain baseline risk of exacerbations, the net

benefit–harm index indicates whether roflumilast increases or decreases the occurrence of patient-centered outcomes overall (weighted by relative importance of outcomes) compared with placebo over 1 year. A positive index indicates that roflumilast provides more benefit than harm. We used simulation to calculate the probability of roflumilast being beneficial as the probability that the index is positive. In sensitivity analyses, we examined the impacts of the severity of exacerbations on the index. Details of the Gail approach are provided in the online appendix.

RESULTS
Data inputs

Table 1 lists the data selected for the benefit–harm assessment of roflumilast. Treatment effect estimates of roflumilast on exacerbations are based on data from the 'pivotal studies pool' of the FDA documents. It consisted of two pivotal RCTs that focused on a population with severe COPD and a history of exacerbations, which reflected the indication for roflumilast.[13] In all other RCTs the inclusion criteria did not require participants to have a history of exacerbations and exacerbations were not the primary outcome. Treatment effect estimates on harms are based on data from the 'COPD safety pool' of the FDA documents, which consisted of 14 RCTs. The harms associated with roflumilast are likely to be independent of the history of exacerbations, so we did not restrict the safety data to the pivotal RCTs. For sensitivity analysis focusing on severe exacerbations, we used the specific treatment effect for severe exacerbations as the outcome for the analysis.

Estimates for the incidence of depression[14] and weight loss[15] are based on observational studies in patients with COPD. Estimates for the incidence of acute pancreatitis[16] and suicide[17] are from observational studies or surveillance of general populations because these are more rare events for which COPD-specific data are not available or are very imprecise. Baseline risks for other harm outcomes where we could not find appropriate data from observational studies are based on the placebo group in the FDA's 'COPD safety pool'.[11] Estimates of mortality stratified by age (<65 years or ≥65 years) and sex are from 10 COPD cohorts with 13 914 patients (1350 deaths).[18] As the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study suggested,[19] around 70% of patients with ≥1 exacerbations in year 1 (ie, those who would potentially qualify for roflumilast) had at least one exacerbation in year 2 of the study. To cover a realistic spectrum of COPD patients with different baseline risks, we performed the analysis for patients at 30%, 60% or 90% risk for at least one moderate or severe exacerbation per year, respectively. In sensitivity analysis restricted to the prevention of severe exacerbations, we considered three different levels of baseline risk (10%, 20% or 30% risk for at least one severe exacerbation per year) because that reflects a range around the risk of severe exacerbations observed in the control group of the pivotal trials (16%).

The different approaches to assigning weight (relative importance of outcomes) are shown in table 1. We considered first equal weights (1.0) for all outcomes, and then weights of 1.0 for life-threatening outcomes, 0.5 for serious and 0.1 for mild outcomes, a similar approach to that proposed by Gail.[12] In order not to overestimate the harms, we considered smaller weights (0.25 or 0.05) for those harm outcomes that tend to occur together (eg, patients may have both depression and anxiety). For sensitivity analysis focusing on severe exacerbations, we considered the

Table 1 Data for the benefit–harm assessment of roflumilast for patients with COPD

Numbers of patients with ≥1 event, person-years and relative risks of roflumilast for patients with COPD[11]*

Type of outcome	Number of patients with ≥1 event		Person-year		Relative risk (95% CI)
	Roflumilast 500 μg	Placebo	Roflumilast 500 μg	Placebo	
Moderate or severe exacerbation	717	821	1186	1240	0.91 (0.82 to 1.01)
Severe exacerbation (for sensitivity analysis)	157	198	1186	1240	0.83 (0.67 to 1.03)
Acute pancreatitis	5	1	3261	3405	5.22 (0.58 to 246.93)
Insomnia	178	61	3261	3405	3.05 (2.27 to 4.15)
Anxiety	82	44	3261	3405	1.95 (1.33 to 2.87)
Depression	80	49	3261	3405	1.70 (1.18 to 2.48)
Suicide (completed)†	2	0	3261	3405	6.00
Diarrhoea	585	143	3261	3405	4.27 (3.55 to 5.17)
Nausea	297	79	3261	3405	3.93 (3.05 to 5.10)
Weight loss	394	101	3261	3405	4.07 (3.27 to 5.12)
Headache	266	110	3261	3405	2.52 (2.01 to 3.18)
Dizziness	139	65	3261	3405	2.23 (1.65 to 3.05)

Incidence rates and mortality rates (per 1000 person-years) without roflumilast for patients with COPD

Type of outcome	Incidence rate	Type of outcome	Incidence rate
Acute pancreatitis[16]	0.077	Weight loss[15]	13.4
Insomnia[11]	17.9	Headache[11]	32.3
Anxiety[11]	12.9	Dizziness[11]	19.1
Depression[14]	16.2	Mortality[18]	
Suicide (completed)[17]	0.124	Men	
Diarrhoea[11]	42.0	Age <65	87.8
Nausea[11]	23.2	Age ≥65	106.4
		Women	
		Age <65	72.1
		Age ≥65	85.2

Weights (relative importance): numerically (eg, 0.5 as used in analysis) and visualised from lowest (◖) to highest importance (••••••••••)

Type of outcome	Analysis I	Analysis II	Analysis III (main analysis)	Sensitivity analysis
	Equal weights	Weights based on importance of outcomes	Weights based on importance and co-occurrence of harm outcomes	Analysis focusing on severe exacerbations
Exacerbation	1.0 ••••••••••	0.5 •••••	0.5 •••••	1.0 ••••••••••
Acute pancreatitis	1.0 ••••••••••	0.5 •••••	0.5 •••••	0.5 •••••
Insomnia	1.0 ••••••••••	0.5 •••••	0.25 •••◖	0.25 •••◖
Anxiety	1.0 ••••••••••	0.5 •••••	0.25 •••◖	0.25 •••◖
Depression	1.0 ••••••••••	0.5 •••••	0.25 •••◖	0.25 •••◖
Suicide (completed)	1.0 ••••••••••	1.0 ••••••••••	1.0 ••••••••••	1.0 ••••••••••
Diarrhoea	1.0 ••••••••••	0.1 •	0.05 ◖	0.05 ◖
Nausea	1.0 ••••••••••	0.1 •	0.05 ◖	0.05 ◖
Weight loss	1.0 ••••••••••	0.1 •	0.05 ◖	0.05 ◖
Headache	1.0 ••••••••••	0.1 •	0.05 ◖	0.05 ◖
Dizziness	1.0 ••••••••••	0.1 •	0.05 ◖	0.05 ◖

*We estimated the treatment effects for exacerbations based on the 'pivotal studies pool' (including trials M2-124 and M2-125). We estimated the treatment effects for other harm outcomes based on the 'COPD safety pool' (including trials FK1-101, FK1-103, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128, and IN-108).
†The relative risk for suicide (completed) was not estimable. We assumed the relative risk was 6.00.

same weights as in our main analysis but changed the weight for exacerbations from 0.5 to 1.0.

Benefit–harm assessment

Table 2 shows the expected number of cases for the 11 outcomes in 10 000 men aged <65 years treated with and without roflumilast over 1 year, stratified by the patients' baseline risk of moderate to severe exacerbations. For example, in men aged <65 years with a baseline risk where 60% of patients have at least one moderate or severe exacerbation over the year, 4055 patients are expected to have at least one exacerbation in the treatment group and 4338 patients in the placebo group (accounted for mortality using Gail approach). Hence, moderate to severe exacerbations are prevented in 284 patients if 10 000 patients are treated with roflumilast. However, at the same time, four cases of acute pancreatitis are expected in the treatment group while one case is expected in the placebo group. Thus, there are three excess cases of acute pancreatitis. As the patients' baseline risk of moderate to severe exacerbations increases, more cases of exacerbation would be prevented (positive numbers) whereas the harms would remain the same (negative numbers).

In table 3 the benefits and harms are combined (ie, net benefit–harm index using the established Gail approach) for men and women in different age groups (<65 years or ≥65 years) with a varying baseline risk of moderate to severe exacerbations. We conducted three types of analyses using different weights as shown in table 1, where we weighted the outcomes equally (analysis I), based on the importance of outcomes (analysis II), or based on both the importance and co-occurrence of harm outcomes (analysis III, main analysis). For example, in men aged <65 where 60% of patients have at least one moderate or severe exacerbation per year, the net benefit–harm index is −148 with a 0.0% probability that the index is positive and roflumilast beneficial. We found that roflumilast had no net benefit in every scenario in table 3 (patients at different baseline risks of moderate or severe exacerbations), and the probabilities

that the index is positive all equal 0.0%. We found that sex and age had little effect on the estimates of the net benefit–harm index.

We also conducted a sensitivity analysis focusing on severe COPD exacerbations (table 3). Roflumilast was found to be beneficial, as the indexes suggest, in some patients with an elevated baseline risk of severe exacerbations. Figure 1 shows that the probability that the index is positive is greater than 50% if the patients' baseline risk of severe exacerbations is greater than 22%.

DISCUSSION

Our analyses showed that roflumilast has no net benefit for younger and older men and women with COPD and a history of moderate to severe exacerbations irrespective of how the benefit and harm outcomes were weighted and irrespective of the baseline risk for moderate to severe exacerbations. However, when we restricted the analysis to severe exacerbations, we found that roflumilast provides more benefit than harm above a baseline risk of 22% for a severe exacerbation over the course of a year.

Our results reflect the complicated regulatory history for PDE$_4$ inhibitors where concerns about gastrointestinal, neurological and psychiatric harms delayed approval of roflumilast.[20] The FDA provides a quantitative benefit–harm assessment in their publicly available statistical review of roflumilast,[21] but the analysis only considered gastrointestinal harms, did not consider different baseline risks or competing risks, and made no attempt to provide an estimate of net benefit (ie, a summary of benefits and harms). The FDA statistical review explicitly stated that the benefit–harm assessment is up to clinical judgement, but the FDA medical review and the transcript of the advisory committee meeting did not entail a quantitative assessment or a discussion of the benefit–harm balance.[11] [22] In our analysis, the evidence for each key element (treatment effects, baseline risks, importance of outcomes and competing risks) is explicitly laid out and considered simultaneously, which allows consideration

Table 2 Expected numbers of cases (patients with ≥1 events) over 1 year for every 10 000 patients (men, age <65 years) treated with and without roflumilast

Type of outcome	Patients' projected 1-year risk of having ≥1 moderate or severe COPD exacerbations								
	30%			60%			90%		
	Roflumilast	Placebo	Number of cases (patients with ≥1 event) prevented or caused*	Roflumilast	Placebo	Number of cases (patients with ≥1 event) prevented or caused*	Roflumilast	Placebo	Number of cases (patients with ≥1 event) prevented or caused*
Moderate or severe exacerbation	2299	2487	188	4055	4338	284	5397	5718	321
Acute pancreatitis	4	1	−3	4	1	−3	4	1	−3
Insomnia	509	170	−339	509	170	−339	509	170	−339
Anxiety	237	123	−115	237	123	−115	237	123	−115
Depression	260	154	−106	260	154	−106	260	154	−106
Suicide (completed)	7	1	−6	7	1	−6	7	1	−6
Diarrhoea	1574	394	−1180	1574	394	−1180	1574	394	−1180
Nausea	834	220	−615	834	220	−615	834	220	−615
Weight loss	508	127	−381	508	127	−381	508	127	−381
Headache	751	304	−446	751	304	−446	751	304	−446
Dizziness	399	181	−218	399	181	−218	399	181	−218

*Positive number indicates cases prevented and negative number indicates cases caused by roflumilast.

Table 3 Net benefit–harm index for treatment of COPD with roflumilast

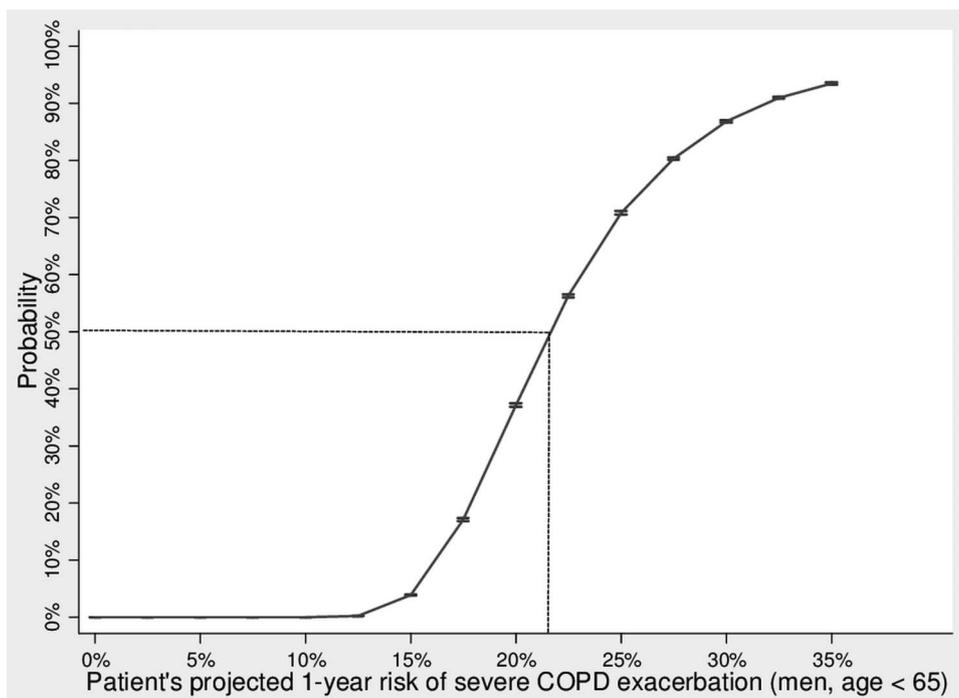**Net benefit–harm index* per 10 000 patients treated over 1 year by patient profiles**

	Patients' projected 1-year risk of having ≥1 moderate or severe COPD exacerbations											
	30%				60%				90%			
	Men		Women		Men		Women		Men		Women	
Type of analysis	Age <65	Age ≥65	Age <65	Age ≥65	Age <65	Age ≥65	Age <65	Age ≥65	Age <65	Age ≥65	Age <65	Age ≥65
Analysis I: Equal weights	−3221 (0.0%)†	−3192 (0.0%)	−3246 (0.0%)	−3225 (0.0%)	−3125 (0.0%)	−3097 (0.0%)	−3150 (0.0%)	−3129 (0.0%)	−3088 (0.0%)	−3059 (0.0%)	−3112 (0.0%)	−3092 (0.0%)
Analysis II: Weights based on importance of outcomes	−477 (0.0%)	−473 (0.0%)	−481 (0.0%)	−478 (0.0%)	−430 (0.0%)	−426 (0.0%)	−433 (0.0%)	−430 (0.0%)	−411 (0.0%)	−407 (0.0%)	−414 (0.0%)	−411 (0.0%)
Analysis III (main analysis): Weights based on importance and co-occurrence of harm outcomes	−195 (0.0%)	−194 (0.0%)	−197 (0.0%)	−196 (0.0%)	−148 (0.0%)	−146 (0.0%)	−149 (0.0%)	−148 (0.0%)	−129 (0.0%)	−127 (0.0%)	−130 (0.0%)	−129 (0.0%)
	Patients' projected 1-year risk of having ≥1 severe COPD exacerbations											
	10%				20%				30%			
Sensitivity analysis focusing on severe exacerbations	−140 (0.0%)	−139 (0.0%)	−141 (0.0%)	−140 (0.0%)	−16 (37.6%)	−16 (37.5%)	−16 (37.0%)	−16 (37.1%)	85 (86.9%)	85 (87.0%)	86 (86.9%)	85 (87.0%)

*Negative values of the index = roflumilast is harmful (harms outweigh benefits); positive values of the index = roflumilast is beneficial (benefits outweigh harms).
†The numbers in parentheses are the probability that the index is positive (the probability that roflumilast is beneficial).

of different scenarios when roflumilast may provide more benefit than harm and when it may not.

In order to assess whether our analyses were robust to the selection of data sources, we conducted a series of analyses. We varied the relative weighting of outcomes, arguably the most controversial part of any benefit-harm assessment, from treating all outcomes the same (ie, assigning the same weights) to an approach where we considered some harms of less importance and where we accounted for the joint occurrence of harm outcomes in order not to overestimate harms. Exacerbations

received a substantial weight in all analyses. Of note, a weight of 0.5 for exacerbations in the main analysis did not minimise their importance because all of the harm outcomes except for suicide received the same or less weight. Although suicide is rare and had a minimal impact on the benefit–harm balance, we considered it most consequential and therefore assigned the largest weight. We did not consider using different treatment effects because we believed that the pivotal and safety pool of the FDA RCTs provided the most valid evidence. Also, we did not consider different baseline risks for harm outcomes since

Figure 1 The Figure shows the probability that the net benefit-harm index is positive (benefits outweigh harms) when treating patients with varying projected 1-year risk of severe COPD exacerbation.

COPD-specific estimates for some gastrointestinal, neurological and psychiatric outcomes are relatively scarce. The observational studies and the placebo groups we identified are likely to provide the best available evidence. However, it still may be reasonable to challenge our decisions about data sources, which highlights the importance of using a comprehensive and transparent approach for quantitative benefit–harm assessment.

We believe that the results of this study will aid guideline developers to make evidence-based recommendations. The available scientific evidence and the benefit–harm balance are among the key elements for developing practice recommendations, as outlined in the frequently used frameworks such as the Grading of Recommendations Assessment, Development and Evaluation.[23][24] Based on our analysis, the benefit–harm balance is not favourable when looking at the entire group of COPD patients with a history of prior exacerbations, with a probability of roflumilast to provide more net benefit than harm approximating 0%. A guideline panel may consider issuing a strong or at least a weak recommendation against the use of roflumilast in patients with COPD with a history of moderate exacerbations. However, for patients at high risk of a severe exacerbation, a guideline panel may come up with a weak or even strong recommendation for using roflumilast depending on cost and local circumstances. Our considerations of possible recommendations described here are not meant to be directive, but they illustrate the usefulness of having separate quantitative estimates for the benefit–harm balance according to the risk and severity of exacerbations.[25]

One strength of our study is the careful identification of the best available evidence. By using FDA data and data from large observational studies, we went considerably beyond the published RCTs and the Cochrane review, respectively, and relied upon the best available evidence. By using trial summary data released by the FDA, we believe that we are less prone to publication bias and, since these trials were conducted by the same manufacturer, the heterogeneity across trials is likely to be limited. Another strength is the use of a transparent approach for quantitative benefit–harm assessment that allows for sensitivity analyses as presented here and additional sensitivity analyses in the future. Also, we considered the statistical uncertainty of treatment effects and baseline risks for outcomes following the Gail approach. This allowed for assessment of a wide variety of scenarios for different patient groups and sources of evidence to facilitate identification of a risk-stratified subgroup of patients who may benefit from an intervention.

A weakness of this analysis is the incomplete adjustment for the joint distribution of outcomes. We accounted for death as a competing risk and accounted for the co-occurrence of harm outcomes. Ideally, observed correlations of all outcomes involved could inform the analyses, but this requires availability of and access to individual patient data.[26] We based our analyses on RCTs that compared roflumilast with placebo and did not consider recent or ongoing RCTs that investigate roflumilast as add-on treatment to inhaled agents. In these RCTs the treatment benefits are likely to be smaller with roflumilast compared with the evidence considered here. We selected evidence for harms from a larger pool of trials that is more comprehensive, but the harm outcomes (eg, psychiatric events) may not be uniformly captured across these trials. We modelled the benefit–harm balance in 1 year for our analysis, but the time horizon would not be sufficient to include all potential harms or benefits caused by roflumilast that might occur later.

Finally, some may argue that there is insufficient evidence to attribute pancreatitis and suicide to roflumilast since the numbers of events are so small. We agree, but decided to include these outcomes for greater transparency and because benefit–harm models should include all outcomes that would be potentially important for decision makers. As we considered the low precision around the effect estimates for these outcomes, we show their (small) impact on the benefit–harm balance. Also, one may argue that weight loss can be beneficial to some patients, but we treated it as harm because the FDA considered weight loss as an adverse event. We have followed this approach but assigned a relatively small weight to weight loss in the analysis. We did not consider lung function in our benefit–harm assessment because it is a surrogate for patient important outcomes we already included in the analyses. We did not consider health-related quality of life because it combines the consequences of exacerbation avoidance and harms, whereas we were interested in specific benefit and harm outcomes and their individual contribution to the benefit–harm balance.

In conclusion, our systematic and transparent benefit–harm assessment of roflumilast for patients with COPD with a history of exacerbations suggests that roflumilast has no net benefit for most patients. However, if patients are at a high 1-year risk of severe exacerbations (>22%), roflumilast is likely to provide more benefit than harm. Guideline developers should consider issuing different recommendations for patients at different risks for moderate and severe exacerbations.

REFERENCES

1 Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2095–128.

2 Vos T, Flaxman AD, Naghavi M, *et al*. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2163–96.

3 Qaseem A, Wilt TJ, Weinberger SE, *et al*. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011;155:179–91.

4 Anzueto A, Sethi S, Martinez FJ. Exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007;4:554–64.

5 Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012;379:1341–51.

6 Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet* 2009;374:744–55.

7 Loukides S, Bartziokas K, Vestbo J, *et al*. Novel anti-inflammatory agents in COPD: targeting lung and systemic inflammation. *Curr Drug Targets* 2013;14:235–45.

8 European Medicines Agency. European Public Assessment Report (EPAR) for Daliresp. 2011. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002398/human_med_001415.jsp&mid=WC0b01ac058001d124 (accessed 29 Mar 2013).

9 US Department of Health and Human Services. Food and Drug Administration. Approval package for: application number: 022522Orig1s000. 2011. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000Approv.pdf (accessed 29 Mar 2013).

10 Chong J, Poole P, Leung B, *et al*. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;(5):CD002309.

11   US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Medical reviews. Application number: 022522Orig1s000. 2010. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000MedR.pdf (accessed 29 Mar 2013).

12   Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91:1829–46.

13   Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374:685–94.

14   Schneider C, Jick SS, Bothner U, et al. COPD and the risk of depression. Chest 2010;137:341–7.

15   Schneider C, Jick SS, Bothner U, et al. Reflux disease, gastrointestinal ulcer or weight loss in patients with COPD. COPD 2010;7:172–8.

16   Levy P, Barthet M, Mollard BR, et al. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. Gastroenterol Clin Biol 2006;30:838–44.

17   Centers for Disease Control and Prevention. National Center for Injury Prevention and Control. National Suicide Statistics at a Glance. http://www.cdc.gov/ViolencePrevention/suicide/statistics/index.html (accessed 29 Mar 2013).

18   Puhan MA, Hansel NN, Sobradillo P, et al. Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. BMJ Open 2012;2(6). doi: 10.1136/bmjopen,2012-002152.

19   Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128–38.

20   Puhan M. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2011;(8):ED000028.

21   US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Statistical reviews. Application number: 022522Orig1s000. 2010. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000StatR.pdf (accessed 29 Mar 2013).

22   US Department of Health and Human Services. Food and Drug Administration. Transcript for the April 7, 2010 Meeting of the Pulmonary-Allergy Drugs Advisory Committee. 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM212606.pdf (accessed 29 Mar 2013).

23   Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:726–35.

24   Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction: GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.

25   Yu T, Vollenweider D, Varadhan R, et al. Support of personalized medicine through risk-stratified treatment recommendations—an environmental scan of clinical practice guidelines. BMC Med 2013;11:7.

26   Puhan MA, Singh S, Weiss CO, et al. A framework for organizing and selecting quantitative approaches for benefit-harm assessment. BMC Med Res Methodol 2012;12:173,2288-12-173.

Benefits and harms of roflumilast in moderate to severe chronic obstructive pulmonary disease

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Appendix

Gail et al. approach to benefit-harm assessment

Gail et al.[1] developed an approach to benefit-harm assessment that combines data on treatment effects, baseline risks, and relative importance of outcomes to provide a net benefit-harm index for decision-making. For a COPD patient at certain age, sex and with a certain baseline risk of exacerbations at treatment initiation, we can use this approach to calculate the net benefit-harm index that indicates whether roflumilast increases or decreases the occurrence of patient-centered outcomes overall (weighted by relative importance of outcomes) as compared to placebo over one year.

To perform this approach, we first calculate the number of cases expected ($N_{X, p}$) without roflumilast for each outcome per 10,000 patients over one year, considering death as a competing risk. We calculate the numbers using equation (1) with the data on incidence rates and mortality rates stratified by age and sex:

(1) $N_{X, p} = 10{,}000*[I_X/(I_X+M)]*\{1-\exp[-1*(I_X+M)]\}$

where $N_{X, p}$ is the expected number of cases for a specific outcome x per 10,000 patients over one year without roflumilast. I_X is the incidence rate for outcome x (baseline risk) and M is the mortality rate.

We can then calculate the corresponding number of cases expected ($N_{X, t}$) per 10,000 patients with COPD if treated with roflumilast over one year following equation (2):

(2) $N_{X, t} = 10{,}000*[R_X*I_X/(R_X*I_X+M)]*\{1-\exp[-1*(R_X*I_X+M)]\}$

where Nx, t is the expected number of cases for a specific outcome x per 10,000 patients with COPD if treated with roflumilast over one year. I_X is the incidence rate for outcome x and M is the mortality rate. In contrast to equation (1), the relative risk of roflumilast on outcome x (R_X) is applied in equation (2).

We use equation (3) to calculate the differences (N_X) in the numbers of cases with and without roflumilast ($N_{X,p} - N_{X,t}$):

(3) $N_X = N_{X,p} - N_{X,t}$

Using equation (4), we calculate a net benefit-harm index as the sum of the difference in cases for each outcome weighted by their relative importance:

(4) $Index = \Sigma(W_X * N_X)$

where Nx is the difference for outcome x and W_X is the weight (relative importance) for outcome x.

The index is a synthesis of all data elements and represents a net benefit-harm comparison. A positive index indicates that roflumilast provides more benefit than harm, and a negative index indicates that roflumilast provides more harm than benefit. As described by Gail et al., we can use simulation to consider the statistical uncertainty (random variability) of the treatment effects for the outcomes.[1] We obtain 10,000 independent samples for each net benefit-harm index (per age, sex and baseline risk of exacerbations) to calculate the probability of roflumilast being beneficial as the proportion of estimates that are positive. In this study, we calculated the net benefit-harm indexes for different patient profiles and using different relative weights. The simulation was done using R statistical software version 3.0.1.

Reference

1. Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999;91(21):1829-46.